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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/679,147	10/05/2000	Tomoki Todo	066683/0188B	7711

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 07/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/679,147	TODO ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7-9,12-16,19,21,23,33,35-37,48,49,52,54,55 and 58-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7-9,12-16,19,21,23,33,35-37,48,49,52,54,59 and 61* is/are rejected.

7)☒ Claim(s) *55,58,60 and 62* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/13/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 5/13/04 has been entered. Claims 2-6, 10-11, 17-18, 22, 24-32, 34, 38-47, 50-51, and 56-57 are canceled, and new claims 58-62 have been added. Claims 1, 7-9, 12-16, 19, 21, 23, 33, 35-37, 48-49, 52, 54-55, and 58-62 are currently pending and under examination. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in previous office actions.

Claim Rejections - 35 USC § 112

The rejection of original, amended, or new claims 1, 7-9, 12-16, 19, 21, 23, 33, 35-37, 48-49, 52, 54, 59 and 61 under 35 U.S.C. 112, first paragraph, for scope of enablement, is maintained in part. Applicant's amendments and arguments have been fully considered but have not been found persuasive in overcoming the remaining grounds of rejection for reasons of record as discussed in detail below.

The previous office action identified the following issues for reasons of record: 1) lack of enablement for making and using soluble co-stimulatory molecules other than B7-1-Ig or B7-2-Ig; 2) lack of enablement for the use of vectors other than HSV vectors; and 3) lack of enablement for vectors capable of "targeting" particular types of cells. Applicant's amendments to the claims have overcome the rejection based on issues 2) and 3).

The rejection of record regarding issue 1) stands. The applicant argues that IgG is not a required component of a soluble costimulatory B7 molecule and that the office has not provided evidence in support of their position that soluble costimulatory B7 molecules other than B7-1-Ig or B7-2-Ig are not enabled by the specification. The application further argues that Fields et al. demonstrates how to make a soluble B7 molecule and that the presence of the Ig spacer in the soluble B7 molecules of Fields are not required for solubility.

In response, the previous office action have pointed out that while the specification provides guidance for making a fusion protein encoding the B7-1 extracellular domain operably linked to the Fc portion of human IgG1, the specification provides no guidance for making any soluble co-stimulatory that does not contain IgG Fc. The specification fails to teach or describe how any membrane bound co-stimulatory molecules of the B7 family can be modified to generate a soluble form of the protein without creating an Ig-fusion such that the resulting soluble B7 is capable of binding to its receptors on T cells and contributing to T cell activation. The specification further does not provide sufficient guidance for making a soluble co-stimulatory molecule with two extracellular domains or for making a soluble co-stimulatory molecule which is a dimer other than by making a B7-Ig fusion protein. The applicant is reminded that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991). The instant specification fails to provide the requisite disclosure for how to make a soluble costimulatory B7 molecule capable of activating T cells other than by fusing the extracellular domain of the B7 molecule to the Fc portion of IgG.

Turning to the state of the art regarding making and using soluble costimulatory molecules, the previous office actions pointed out that publications by Kato et al., Kanner et al., Noelle et al., and Hurtado et al. previously cited by the applicants, while demonstrating that it was within the skill of the artisan to make a soluble co-stimulatory molecule comprising the extracellular domain of a co-stimulatory molecule and IgG, does not provide enablement for making soluble co-stimulatory molecules that do not contain IgG. None of these publications teach or suggest other ways of producing a soluble costimulatory molecule that is capable of binding to its receptor and mediating T cell activation other than making an Ig fusion protein. Fields et al., now cited by the applicants, does not provide any more knowledge that the previously cited papers. Fields et al. is also solely directed to making and using a soluble B7-1-Ig fusion protein and a soluble B7-2-Ig fusion protein. Fields does not teach or suggest that the extracellular domain of either B7-1 or B7-2 by itself is capable of correctly folding such that the extracellular domain alone is capable of binding to CD28 or CTLA-4 and activating T cells. Applicant's reliance on Fields for showing that the Ig portion of the fusion protein were not required to produce a soluble B7 molecule is therefore misplaced. Thus, the state of the art at the time of filing for making a soluble costimulatory molecule, as reflected by the publications by Kato et al., Kanner et al., Noelle et al., Hurtado et al., and Fields et al., was to make a fusion protein comprising the extracellular domain of the costimulatory molecule and the Fc portion of IgG. Please note that the Federal Circuit has stated that:

> ..a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, **when**

> **there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art.** It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997) (emphasis added).

Thus, in the instant case, neither the specification nor the prior art provide the requisite teachings for how to make a soluble costimulatory molecule of the B7 family capable of activating a T cell response other than by making a fusion protein comprising the extracellular domain of B7 and the Fc portion of IgG.

It is also noted that the office has analyzed the specification in direct accordance to the factors outlined in In re Wands, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, and 5) the presence or absence of working examples, and presented detailed scientific reasons supported by publications from the prior art for the finding of a lack of enablement in the instant. It is also noted that case law including the *Marzocchi* decision sanctions both the use of sound scientific reasoning and printed publications to support a holding of non-enablement (see *In re Marzocchi* 169 USPQ 367, and *Ex parte Sudilovsky* 21 USPQ2d 1702). Ultimately, 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). For the reasons discussed in detail above and in previous office actions, the instant specification fails to provide an enabling disclosure which reasonably correlates with the scope of the claims as written.

Regarding applicant's argument that Kwon et al. provides evidence that the skilled artisan would have been able to use soluble co-stimulatory molecules of the B7 family, Kwon et al. is concerned with blocking CTLA-4 using anti-CTLA-4 antibodies. Antibodies are not soluble costimulatory factors of the B7 family. Kwon et al. does not teach, suggest, or even mention B7 or the B7 family of molecules, and further does not contemplate soluble costimulatory factors of the B7 family. Thus, a nexus cannot be made between the teachings of Kwon et al. and the instant claims as written.

Regarding applicant's comments as to B7 family members other than B7-1 and B7-2, it is noted that the specification does not teach costimulatory factors of the B7 family other than B7-1 or B7-2. Page 3 of the specification vaguely states, "[b]y the use of soluble costimulatory factors, preferably of the B7 family, such as B7-1, the present invention overcomes the problem of T-cell anergy towards poorly immunogenic or nonimmunogenic tumors". This section clearly does not describe or identify other members of the "B7 family". Further, regarding applicant's citation of Henry et al. that members of the B7 family share distinctive domain organization and play a role in T cell activation, Henry et al. does not in fact provide such teachings. Henry et al. does indeed show that molecules other than B7-1 and B7-2 share a similar domain organization which can be used to identify a group of structurally related molecules. However, these molecules are not functionally related. Other than B7-1 and B7-2, none of the other molecules identified in Henry et al. are costimulatory factors. Butyrophilin and the BT family members apparently participate in superoxide regulation and are expressed in mammary glands.

Myelin oligodendrocyte glycoprotein is expressed exclusively in the CNS and its function is unknown, and chicken B-G polypeptides may potentially be involved in recruiting macrophages.

Thus, clearly, the structural relationship between putative B7 family members does not correlate with a functional relationship. There is no evidence that any of these molecules other than B7-1 and B7-2 bind to CD28 and CTLA-4 or are involved in T cell activation as costimulatory factors. Therefore, applicant's arguments are not found persuasive.

The rejection of claim 57 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn in view of applicant's amendments to the claims.

Applicant's amendment has necessitated the following new grounds of rejection.

Claims 8-9 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1, from which claims 8 and 9 depend, has been amended to recite a herpes simplex virus vector comprising an expressible nucleotide sequence for a costimulatory molecule in the B7 family. Therefore, in claims 8 and 9, the limitations to the administration of "said nucleotide sequence" is confusing as it is unclear whether the applicant is referring to the herpes simplex virus vector which comprises the nucleotide sequence or the nucleotide sequence by itself. It is suggested that applicant amend claims 8 and 9 to replace "said nucleotide sequence" with "said herpes simplex virus vector".

Allowable Subject Matter

Claims 55, 58, 60, and 62 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. For all official communications, the

technology center fax number is (703) 872-9306. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER